Antithrombotic Therapy in Patients with COVID-19

(Last updated May 12, 2020)

Summary Recommendations

Laboratory Testing:

- In non-hospitalized patients with COVID-19, there are currently no data to support the measurement of coagulation markers (e.g., D-dimers, prothrombin time, platelet count, fibrinogen) **(AIII)**.

- In hospitalized patients with COVID-19, hematologic and coagulation parameters are commonly measured, although there are currently insufficient data to recommend for or against using this data to guide management decisions **(BIII)**.

Chronic Anticoagulant and Antiplatelet Therapy:

- Patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions should continue these medications if they receive a diagnosis of COVID-19 **(AIII)**.

Venous Thromboembolism Prophylaxis and Screening:

- For non-hospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for prevention of venous thromboembolism (VTE) or arterial thrombosis unless there are other indications **(AIII)**.

- Hospitalized adults with COVID-19 should receive VTE prophylaxis per the standard of care for other hospitalized adults **(AIII)**. A diagnosis of COVID-19 should not influence a pediatrician's recommendations about VTE prophylaxis in hospitalized children **(BIII)**. Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual standard of care for patients without COVID-19 **(AIII)**.

- Reported incidence of VTE in hospitalized patients with COVID-19 varies. There are currently insufficient data to recommend for or against the use of thrombolytics or increasing anticoagulant doses for VTE prophylaxis in hospitalized COVID-19 patients outside the setting of a clinical trial **(BIII)**.

- Hospitalized patients with COVID-19 should not routinely be discharged on VTE prophylaxis **(AIII)**. Using Food and Drug Administration-approved regimens, extended VTE prophylaxis can be considered in patients who are at low risk for bleeding and high risk for VTE as per protocols for patients without COVID-19 (see text for details on defining at-risk patients) **(BI)**.

- There are currently insufficient data to recommend for or against routine deep vein thrombosis screening in COVID-19 patients without signs or symptoms of VTE, regardless of the status of their coagulation markers **(BIII)**.

- For hospitalized COVID-19 patients, the possibility of thromboembolic disease should be evaluated in the event of rapid deterioration of pulmonary, cardiac, or neurological function, or of sudden, localized loss of peripheral perfusion **(AIII)**.

Treatment:

- Patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease at a time when imaging is not possible should be managed with therapeutic doses of anticoagulant therapy as per the standard of care for patients without COVID-19 **(AIII)**.

- Patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters should be treated with antithrombotic therapy per the standard institutional protocols for those without COVID-19 **(AIII)**.

Special Considerations During Pregnancy and Lactation:

- Management of anticoagulation therapy during labor and delivery requires specialized care and planning and should be managed similarly in pregnant patients with COVID-19 as other conditions that require anticoagulation in pregnancy **(AIII)**.

- Unfractionated heparin, low molecular weight heparin, and warfarin do not accumulate in breast milk and do not induce an anticoagulant effect in the newborn; therefore, they can be used in breastfeeding women with or without COVID-19 who require VTE prophylaxis or treatment **(AIII)**. In contrast, direct-acting oral anticoagulants are not routinely recommended due to lack of safety data **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

Association Between COVID-19 and Thromboembolism

Infection with the novel coronavirus SARS-CoV-2 and the resulting syndrome coronavirus disease (COVID-19) has been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimers.[1,2] In fact, these markers have been associated with worse clinical outcomes.[3,4] Although the true incidence of these complications among those with different severities of disease is not completely defined, there have been reports of increased incidence of thromboembolic disease associated with COVID-19 in patients in the intensive care unit (ICU).[5,6] In a French prospective multicenter cohort of 150 ICU patients, 16.7% had pulmonary embolism despite prophylactic anticoagulation. Patients with COVID-19 and acute respiratory distress syndrome (ARDS) had increased incidence of pulmonary embolism compared to patients without COVID-19-associated ARDS.[6] A Dutch study of 184 ICU patients reported a cumulative incidence of venous thromboembolism (VTE) of 27% (95% confidence interval, 17% to 32%), despite prophylaxis.[7] A study that used routine ultrasounds reported VTE incidence of 69%[5] in those admitted to the ICU. However, other centers have reported lower event rates. An Italian study found a VTE rate of 22.2%.[8] Among 393 patients from New York, only 13 patients (3.3%) experienced VTE; 10 of those patients (7.7%) were mechanically ventilated, and three (1.1%) were not mechanically ventilated.[9] Epidemiologic studies that control for clinical characteristics, underlying comorbidities, prophylactic anticoagulation, and COVID-19-related therapies are needed.

Notably, all of the studies described above relied on clinical findings that were suggestive of thromboembolic events to trigger a diagnosis of thromboembolism. Although the incidence of thromboembolic events, especially pulmonary emboli, can be quite high, there are, as of yet, no published data investigating the utility of routine surveillance for deep vein thrombosis via lower extremity ultrasound. However, for clinicians who routinely perform ultrasound examinations in critically ill patients, adding deep veins to the daily examination could be a useful adjunct to care.

There remains very little prospective data demonstrating the benefits of monitoring coagulation markers or the safety and efficacy of using therapeutic doses of anticoagulants in those with COVID-19 in the absence of other indications. A retrospective analysis of 2,773 patients from a single center in the United States reported in-hospital mortality in 22.5% of patients who received therapeutic anticoagulation and 22.8% of patients who did not receive anticoagulation. The study further reported that in a subset of 395 mechanically ventilated patients, 29.1% who received anticoagulation and 62.7% who did not receive anticoagulation died. The study had important limitations: it lacked details on patient characteristics, indications for anticoagulant initiation, and descriptions of other therapies that the patients received that may have influenced mortality. In addition, the authors did not discuss the potential impact of survival bias on the study results. For these reasons, the data are not sufficient to influence standard of care, and this study further emphasizes the need for prospective trials to define the risks and potential benefits of therapeutic anticoagulation in patients with COVID-19.[10]

A number of randomized controlled trials have been developed to evaluate the risks and benefits of anticoagulation in patients with COVID-19 (visit *ClinicalTrials.gov* for the current list of trials). Interim guidance on recognizing and managing coagulopathy in patients with COVID-19 has been released by the International Society of Thrombosis and Haemostasis (ISTH).[11] The American Society of Hematology has developed guidance statements about coagulopathy and venous thromboembolism. An additional paper that outlines issues related to thrombotic disease with implications for prevention and therapy has been endorsed by the ISTH, the North American Thrombosis Forum, the European Society of Vascular Medicine, and the International Union of Angiology.[12]

Monitoring Coagulation Markers in Patients with COVID-19:

- Non-hospitalized patients with COVID-19 should not routinely be tested for measures of coagulopathy, such as D-dimer level, prothrombin time, fibrinogen level, and platelet count **(AIII)**. Although abnormalities of these markers have been associated with worse outcomes, there is a lack of prospective data demonstrating that they can be used for risk stratification in those who are asymptomatic or those with mild SARS-CoV-2 infection.

- Hematologic and coagulation parameters are commonly measured in hospitalized patients with COVID-19. Nevertheless, there are currently insufficient data to recommend for or against using such data to guide management decisions **(BIII)**.

Managing Coagulopathy in Patients with COVID-19

Selection of Anticoagulant or Antiplatelet Drugs for Patients with COVID-19:[13]

- Any time anticoagulant or antiplatelet therapy is being used, consideration must be given to potential drug-drug interactions with other concomitant drugs **(AIII)**. The University of Liverpool has collated a list of drug interactions.

- Low molecular weight heparin or unfractionated heparin may be preferred in hospitalized, critically ill patients because of their shorter half-lives, ability to be administered intravenously or subcutaneously, and fewer drug-drug interactions compared with oral anticoagulants **(AIII)**.

- Outpatients receiving warfarin who are unable to get international normalized ratio monitoring during isolation may be candidates for direct oral anticoagulant therapy. Patients with mechanical heart valves, ventricular assist devices, valvular atrial fibrillation, or antiphospholipid antibody syndrome or patients who are lactating should continue treatment with warfarin therapy **(AIII)**.

Chronic Anticoagulant or Antiplatelet Therapy:

- Patients with COVID-19 who are taking anticoagulant or antiplatelet therapy for underlying medical conditions should continue their treatment unless significant bleeding develops or other contraindications are present **(AIII)**.

Patients with COVID-19 Who Are Managed as Outpatients:

- For non-hospitalized patients with COVID-19, anticoagulant or antiplatelet therapy should not be initiated for VTE prophylaxis or at therapeutic doses **(AIII)**.

Hospitalized Patients with COVID-19:

- For adults who are admitted to a hospital with COVID-19, VTE prophylaxis, unless contraindicated (e.g., a patient has active hemorrhage or severe thrombocytopenia), should be prescribed using the recommendations for patients who have been admitted to a hospital for other indications **(AIII)**. Although data supporting this recommendation are limited, a retrospective study showed reduced mortality in patients who received prophylactic anticoagulation, particularly if the patient had a sepsis-induced coagulopathy score ≥4.[4]

- A recent meta-analysis of COVID-19 infection in children did not discuss venous thromboembolism.[14] Given insufficient data, COVID-19 infection should not change VTE prophylaxis recommendations for hospitalized children **(BIII)**.

- Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the standard of care for those without COVID-19 **(AIII)**. Anticoagulation is routinely used to prevent arterial thromboembolism in patients with heart arrhythmias. Although there are reports

of strokes and myocardial infarction in patients with COVID-19, the incidence of these events is unknown.

- Patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease at a time when imaging is not possible should be managed with therapeutic doses of anticoagulant therapy as per the standard of care for patients without COVID-19 **(AIII)**.

- There are currently insufficient data to recommend either for or against using therapeutic doses of antithrombotic or thrombolytic agents for COVID-19 in patients who are admitted to a hospital **(BIII)**. While there is evidence that multi-organ failure is more likely in patients with sepsis if they develop coagulopathy,[15] there are no convincing evidence to show that any specific antithrombotic treatment will influence outcomes in those with or without COVID-19. Participation in randomized trials is encouraged, if trials are available.

- Patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters should be treated as per the standard institutional protocols for those without COVID-19 **(AIII)**.

Patients with COVID-19 Who Are Discharged from the Hospital:

- Routine post-discharge VTE prophylaxis **is not recommended** for patients with COVID-19 **(AIII)**. However, the benefits of post-discharge prophylaxis for certain high-risk patients without COVID-19 led to the Food and Drug Administration approval of two regimens: rivaroxaban 10 mg daily for 31 to 39 days, and betrixaban 160 mg on Day 1, followed by betrixaban 80 mg once daily for 35 to 42 days.[16,17] Inclusion criteria for the trials that studied these regimens included:

  - Modified IMPROVE-VTE score ≥4; *or*

  - Modified IMPROVE-VTE score ≥2 and D-dimer level >2 times the upper limit of normal;[16] *or*

  - Age ≥75 years; *or*

  - Age >60 years and D-dimer level >2 times the upper limit of normal; *or*

  - Age 40 to 60 years, D-dimer level >2 times the upper limit of normal, and previous VTE event or cancer.[17]

- Any decision to use post-discharge VTE prophylaxis should consider the individual patient's risk factors, including reduced mobility, bleeding risks, and feasibility.

Special Considerations for Pregnancy and Lactation

Several professional societies, including the American Society of Hematology and the American College of Obstetricians and Gynecologists, have guidelines that specifically address management of VTE in the context of pregnancy.[18,19] There is a lack of data on the use of these scoring systems to predict VTE risk in pregnant people. Additionally, the D-dimer level may not be a reliable predictor of VTE in pregnancy, because there is a physiologic increase of D-dimer levels throughout gestation.[20-22]

In general, the preferred anticoagulants during pregnancy are heparin compounds.[2] Because of its reliability and ease of administration, low-molecular weight heparin is recommended rather than unfractionated heparin for prevention and treatment of VTE in pregnancy.[19]

Direct-acting anticoagulants are not routinely used during pregnancy due to the lack of safety data in pregnant people.[18] The use of warfarin for the prevention or treatment of VTE should be avoided in pregnant people, regardless of their COVID-19 status; this is especially true during the first trimester, due to the concern for teratogenicity.

Specific recommendations for pregnant women with COVID-19 include:

- If antithrombotic therapy is prescribed during pregnancy for another indication, this therapy should be continued if the patient receives a diagnosis of COVID-19 **(AIII)**.

- For pregnant patients admitted to the hospital with COVID-19, recommendations for VTE prophylaxis are the same as those for hospitalized nonpregnant patients **(AIII)**.

- Management of anticoagulation therapy during labor and delivery requires specialized care and planning and should be managed similarly in pregnant patients with COVID-19 as other conditions that require anticoagulation in pregnancy **(AIII)**.

Thrombolytic Therapy in Pregnancy:

Due to the potential risk of maternal hemorrhage, during pregnancy, thrombolytic therapy should be reserved for acute pulmonary embolism with life-threatening hemodynamic instability regardless of whether a patient has COVID-19 **(AIII)**.[18]

Lactation:

Unfractionated heparin, low molecular weight heparin, and warfarin do not accumulate in breast milk and do not induce an anticoagulant effect in the newborn; therefore, they can be used in breastfeeding women with or without COVID-19 who require VTE prophylaxis or treatment **(AIII)**.[19] In contrast, direct-acting oral anticoagulants are not routinely recommended due to the lack of safety data **(AIII)**.[18]

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